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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 10/032,717
Filing Date: October 23, 2001
Appellant(s): ABAD ET AL.

Leigh Thorne
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 6 September 2005 appealing from the Office action mailed 6 May 2005.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Hill et al, Functional Analysis of Conserved Histidines in ADP-Glucose Pyrophosphorylase from Escherichia coli, Biochem. Biophys. Res. Comm. (1998) 244:573-577.

Lazar et al, Transforming Growth Factor α: Mutation of Aspartic Acid 47 and Leucine 48 Results in Different Biological Activities, Mol. Cell. Biol. (March, 1988) 8:1247-1252.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

**(a)** Claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52 and 55-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:2 and 10, expression cassettes comprising the nucleic acids, plants and seeds comprising a construct comprising the nucleic acid, and a method of using it to impact a plant pest, does not reasonably provide enablement for any nucleic acid that has 90% identity to SEQ ID NO:1, expression cassettes comprising the nucleic acid, plants and seeds comprising a construct comprising the nucleic acid and a method of using it to impact a plant pest. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to any nucleic acid that has 90%, 93%, 94% or 95% identity to SEQ ID NO:1, expression cassettes comprising the nucleic acids, plants and seeds comprising constructs comprising the nucleic acids, and a method of using the constructs to impact a plant pest.

The instant specification, however, only provides guidance for methods of assaying the

activity of *B. thuringiensis* strain 1218 and lysate against Western corn rootworm and Southern corn rootworm (examples 1 and 2); isolation of crystal protein from the strain and assaying of it for pesticidal activity against western corn rootworm (example 3); identification of two coding regions, *Cry1218-1* and *Cry1218-2* (SEQ ID NO:1 and 3, with SEQ ID NOs:27 and 28 as the genomic clones), isolated by unknown methods, as encoding proteins, SEQ ID NOs:2 and 4, respectively, that have homology to Cry8Ba1 (example 4); production in *E. coli* of truncated proteins, SEQ ID NOs:15 and 17, encoded by SEQ ID NOs:16 and 18, respectively, that are active against southern corn rootworm (example 4); and production of maize-preferred coding sequences of a different truncated version of Cry1218-1 - the nucleic acid is SEQ ID NO:9, which encodes SEQ ID NO:10 (example 5). The specification also teaches making two mutant versions of truncated Cry1218-1 (SEQ ID NO:16), one of which has a truncated N-terminus (comprising amino acids 43-663 of SEQ ID NO:16), and the other in which the 4 amino acid sequence NGSR has been inserted after amino acid 164 - all of these mutant proteins are effective against Colorado potato beetle (example 6) and other mutant proteins (SEQ ID NOs:32, 34, 42 and 46) that have added chymotrypsin cleavage sites - all are more effective against southern and western corn rootworm than Cry1218-1 (example 7). The specification also teaches transformation of maize with SEQ ID NO:9 (examples 8 and 9).

The instant specification fails to provide guidance for nucleic acid that has 90%, 93%, 94% or 95% identity to SEQ ID NO:1, expression cassettes comprising the nucleic acid, plants and seeds comprising a construct comprising the nucleic acid and a method of using it to impact a plant pest.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain Cry8 activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

The specification on pg 28, lines 5-11, suggests making these nucleic acids by making conservative substitutions in the encoded protein. However, making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). The nucleic acids encoding all these mutated proteins, however, would have much greater than 90% identity to the nucleic acids encoding the original protein.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids with 90% identity to SEQ ID NO:1 or that hybridizes to SEQ ID NO:1. Making all possible single amino acid substitutions, in an 3621 nucleotide long nucleic acid like that of SEQ

ID NO:1 would require making and analyzing $19^{3621}$ nucleic acids; these nucleic acids would have about 99.99% identity to SEQ ID NO:1. Because nucleic acids that have 90% identity to SEQ ID NO:1 would have up to 362 nucleotide substitutions, many more than $19^{3621}$ nucleic acids would need to be made and analyzed.

Furthermore, because nucleic acids that have 90% identity to SEQ ID NO:1 would have up to 362 nucleotide substitutions, they could encode proteins with up to 362 amino acid substitutions; these proteins would have 70% identity to the 1206 amino acid long SEQ ID NO:2. The specification provides no guidance for which 362 amino acids to substitute. Thus, undue trial and error experimentation would be required to make the claimed nucleic acids.

Similarly, nucleic acids that have 93% identity to SEQ ID NO:1 would have up to 253 nucleotide substitutions, nucleic acids that have 94% identity to SEQ ID NO:1 would have up to 217 nucleotide substitutions and nucleic acids that have 90% identity to SEQ ID NO:1 would have up to 181 nucleotide substitutions, producing proteins with 79%, 82% and 85% identity, respectively, to the 1206 amino acid long SEQ ID NO:2.

The specification, on pg 65, lines 12-14, indicates that the instant SEQ ID NO:1 has homology to GenBank U04365, which is identical to SEQ ID NO:3 of Michaels et al (1996, US Patent 5,554,534). This nucleotide sequence has 85.1% identity to SEQ ID NO:1; however, it encodes a protein with 79.8% identity to the instant SEQ ID NO:2 (see sequence search report). Thus, this sequence cannot be used as guidance for nucleic acids with 90% identity to SEQ ID NO:1 and that encode proteins with 70% identity to SEQ ID NO:2, as encompassed by the full scope of the claims.

As the specification does not describe the transformation of any plant with any nucleic

acid with 90% identity to SEQ ID NO:1, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those that could control plant pests, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

**(b)** Claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52 and 55-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A full review of the specification indicates that nucleic acids that have 90%, 93%, 94% or 95% identity to SEQ ID NO:1 and that encode Coleopteran-pesticides are essential to the operation of the claimed invention.

The level of skill and knowledge in the art at the time of filing was such that while large number of Coleopteran-pesticides were known, nucleic acids that have 90%, 93%, 94% or 95% identity to SEQ ID NO:1 and that encode such Coleopteran-pesticides were not.

The claim is directed to a genus of nucleic acids that have 90%, 93%, 94% or 95% identity to SEQ ID NO:1. Nucleic acids that have 90%, 93%, 94% or 95% identity to SEQ ID NO:1 would have up to 362 nucleotide substitutions, they could encode proteins with up to 362, 253, 217 or 181 amino acid substitutions relative to the to the 1206 amino acid long SEQ ID NO:2.

The structural features that distinguish Coleopteran-pesticide-encoding nucleic acids that have 90%, 93%, 94% or 95% identity to SEQ ID NO:1 from other that have 90%, 93%, 94% or 95% identity to SEQ ID NO:1 are not described in the specification. The specification recites no structure required for Coleopteran-pesticide activity. The necessary and sufficient structural elements of a protein with Coleopteran-pesticide activity are not described.

The only species described in the specification is SEQ ID NO:1, which encodes SEQ ID NO:2, a truncated version of SEQ ID NO:1, and a few nucleic acids with a few nucleotide substitutions relative to SEQ ID NO:1.

One of skill in the art would not recognize that Applicant was in possession of the necessary common attributes or features of the genus in view of the disclosed species. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO:1 alone is insufficient to describe the claimed genus.

Hence, Applicant has not, in fact, described nucleic acids with 90%, 93%, 94% or 95% identity to SEQ ID NO:1 and that encode a protein pesticidal for at least one pest belonging to the order Coleoptera within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

**(10) Response to Argument**

**(a)** Claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52 and 55-64 do not meet the enablement requirement of 35 USC §112, first paragraph.

Appellant argues that guidance is provided as to what sequence alterations may be made and still provide a pesticidal polypeptide; endotoxin genes are well known in the art, an exemplary sequence was provided, the claimed sequences differ from the exemplary by structural parameters, guidance for determining percent identity is given on pg 33-38, and methods of assay are given (Brief pg 4-5).

However, the specification does not teach how to make nucleic acids encoding Coleopteran pesticidal proteins with 181, 217, 253 or 362 substitutions, as encompassed by the full scope of the claims. Guidance for determining percent identity does not teach the necessary and sufficient structural features of the claimed nucleic acids, and does not teach which amino acids could be substitutive with which other amino acids.

Appellant argues that the specification provides the exemplary sequence SEQ ID NO:1, which encodes the Cry-8-like-δ-endotoxin SEQ ID NO:2; B. thuringiensis δ-endotoxin are very well characterized, quoting portions of the specification which discuss Li et al (Brief pg 6).

However, Li et al only provided guidance for making truncations and insertion of chymotrypsin cleavage sites; Li et al do not provide guidance for making 181, 217, 253 or 362 amino acid substitutions in a 1206 amino acid protein. Furthermore, the protein taught by Li et al is a cry3Aa protein, not a Cry8 protein. The instant inventors did not use Li et al to make 181, 217, 253 or 362 amino acid substitutions in a 1206 amino acid protein to create a Coleopteran pesticidal protein.

Appellant argues that the claims are not require the modification of particular numbers of nucleotides, only that the nucleic acids have a certain percent identity to SEQ ID NO:1 (Brief pg 6, footnote 1).

However, the numbers of nucleotide substitutions are drawn from the claimed percent identity. A nucleic acid with 90% identity to the 3621 nucleotide long SEQ ID NO:1 would have up to 362 nucleotide substitutions relative to SEQ ID NO:1. Nucleic acids with 90% identity to SEQ ID NO:1 could not be made without making 362 nucleotide substitutions. As nucleic acids with 90% identity to SEQ ID NO:1 could encode a protein with 362 amino acid substitutions relative to the 1206 amino acid long SEQ ID NO:2, the specification must teach how to make proteins with 362 amino acid substitutions relative to SEQ ID NO:2.

Appellant argues that that knowledge in the art was used for guidance in making mutations in the Cry8-like proteins, as in Example 6; thus, adequate guidance is provided (Brief pg 7).

However, the only mutations made in Example 6 a truncated Cry1218-1 protein and a protein in which the 4 amino acid sequence NGSR has been inserted after amino acid 164. The full scope of the claims, on the other hand, encompasses nucleic acids encoding proteins in which 181, 217, 253 or 362 amino acid substitutions are made relative to Cry1218-1. Applicant does not teach the making of such proteins.

Appellant argues that the specification teaches several nucleic acids with low percent identity to SEQ ID NO:1 but that encode pesticidal proteins. In Examples 4 and 6, truncated proteins encoded by SEQ ID NO:15 and 19 are described; they have 55% and 51% identity to SEQ ID NO:1, respectively, and is structurally very different from SEQ ID NO:1 (Brief pg 7).

However, while the query match similarity between the truncated proteins encoded by SEQ ID NO:15 and 19 may be 55% and 51% to SEQ ID NO:1, respectively, the query match value is affected by differences in length of the sequences. One of skill in the art would not consider a truncated protein as having 55% identity over its entire length, but would only look at it as a truncated protein. The local match similarity between SEQ ID NO:15 and the first half of SEQ ID NO:1 is 100%. This can be represented as in the following 20 amino acid long "protein" in which the Original amino acids are represented by "O":

| | |
|---|---|
| Original: | OOOOOOOOOOOOOOOOOOO |
| Truncated with 50% query match similarity | OOOOOOOOOO |

One of skill in the art would understand a protein with 50% identity to encompass the following types of proteins, where in the following "S" represents any amino acid other than the original:

| | |
|---|---|
| Original: | OOOOOOOOOOOOOOOOOOO |
| Protein with 50% identity | SOSOOSOOSOSOSOSSSOSO |
| Protein with 50% identity | SOOSOSOSOOSOSSOSSOOS |
| Protein with 50% identity | OSOSOOSOOSOSOSOSOSSO |
| Protein with 50% identity | OOSOOSOOSOSOSOSOSOSO |

Thus, one of skill in the art would not consider SEQ ID NO:15 as teaching which 181, 217, 253 or 362 amino acids to substitute in SEQ ID NO:2.

Appellant argues that Example 6 also teaches the truncated protein encoded by SEQ ID NO:11 which also has a four amino insertion in it and that SEQ ID NO:11 has 56% identity to SEQ ID NO:1. Applicant also argues that the specification teaches a maize-optimized sequence that encodes SEQ ID NO:16 but has less than 69% identity to SEQ ID NO:15 (Brief pg 8).

However, SEQ ID NO:11 only provides guidance for a single insertion of 4 amino acids in the 669 amino acid long SEQ ID NO:16 and does not provide guidance for nucleic acids

encoding proteins with 70% identity to SEQ ID NO:2, which nucleic acids with 90% identity to SEQ ID NO:1 encompass. No amino acid substitutions were made in the protein sequence encoded by SEQ ID NO:15. Nucleic acids encoding SEQ ID NO:16 are enabled, and this is true regardless of their identity to SEQ ID NO:15. What is not enabled is nucleic acids encoding proteins with 181, 217, 253 or 362 amino acid substitutions relative to SEQ ID NO:2, or the full scope of nucleic acids with 90%, 93%, 94% or 95% identity to SEQ ID NO:1.

Appellant argues that it is not necessary to make and use every embodiment within the scope of the claims; they have provided exemplary sequences, variants and fragments, and thus have taught a representative number of species (Brief pg 8-9).

However, the percent identity, relative to SEQ ID NO:2, of the variants taught by the specification do not represent the full scope of the claims. Making a fragment and a single 4 amino acid substitution are not the same thing as making 362 amino acid substitutions.

Appellant argues that experimentation is not undue because it is not necessary to make and use every embodiment; some experimentation is permitted (Brief pg 9-10).

However, assays for the protein are more detailed than assays for enzymatic activity; the latter can often be easily assayed spectrophotographically. The assays detailed in Examples 4, 6 and 7 require expressing the proteins in E. coli, purifying the protein from large scale cultures of the bacteria via affinity chromatography followed by extensive dialysis, and incorporating the protein into the diets of rootworms in replicates of 4, with mortality measured on the $4^{th}$ to $7^{th}$ day (Examples 4, 6 and 7); thus, each assay requires up to two weeks and large quantities of materials. As guidance is not provided for making up to 362 amino acid substitutions in a 1206 amino acid protein, undue trial and error experimentation would be required to make and to

assay vast numbers of nucleic acids in order to find functional proteins that fall within the scope of the claims.

Appellant argues that all the claim 9 requires over claim 1 is the transformation of a plant, which is routine in the art; similarly making the constructs comprising the nucleic acid of claim 1 requires no undue experimentation (Brief pg 10).

However, making the nucleic acids of claims 1-2, 38 and 55-57 requires undue experimentation; thus making plants and constructs comprising them requires undue experimentation. The rejection is not that plant transformation and expression cassettes per se requires undue experimentation, but that making the nucleic acid required for the claimed plants and expression cassettes is undue.

Appellant argues that that it is customary in the art to make and assay sequences, for example by shuffling, as described in US 5,837,458. Applicant also cites Minshull et al and Christians et al, and urges that these methods are designed to generate and test a very large number of variant sequences (Brief pg 10-11).

However, with respect to using DNA shuffling, the specification, on pg 29, suggests using GenBank U04365, which is identical to SEQ ID NO:3 of Michaels et al (1996, US Patent 5,554,534), as the other nucleic acid in shuffling; however, this sequence encodes a protein with 79.8% identity to the instant SEQ ID NO:2. Thus, such a nucleic acid could not be used to generate a nucleic acid that encodes a protein with 70% identity to SEQ ID NO:2. Furthermore, Christians et al did not produce proteins with only 70% identity to the starting protein (see paragraph spanning pg 260-261). Minshull et al teaches that a population should be used as the starting material (pg 284, right column, paragraph 4); the specification does not teach such a

population. Minshull et al also teaches that the activities of chimeric enzymes are not predictable simply by comparing those of the parent enzymes (paragraph spanning pg 288-289); thus, even if the population of starting materials has been provided, making nucleic acids that encode proteins pesticidal to coleopterans and have substitutions within the full scope of the claims is not predictable.

Appellant argues that Dr. Abad in his Declaration states that he would be able to make and use the claimed nucleic acids by making nucleic acids with 90% identity to SEQ ID NO:1 and assaying the activity of the encoded protein and would consider this experimentation routine.; this Declaration is not only an opinion (Brief pg 11).

However, Dr Abad states that it is his understanding that proteins can be produced that share a relatively low degree of sequence identity, "maybe even as low as 70% identity". The Declaration thus only provides opinions, and ones the Declarant is not even sure of. The Declaration provides no factual evidence to support the conclusion of enablement. See *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991), which states "expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement".

Appellant argues that one of skill in the art would be able to use the assays taught in the specification to determine which sequences that meet the sequence identity limitations of the claims encode pesticidal proteins and the amount of experimentation would not be undue; Lazar and Hill illustrate thus (Brief pg 11-12).

However, Lazar and Hill teach that even making single amino acid substitutions is unpredictable; Hill teaches that is true even the substitutions are made based on comparison to

homologous sequences. Thus, making 181, 217, 253 or 362 amino acid substitutions relative to SEQ ID NO:2, as encompassed by the full scope of the claims, would be even more unpredictable.

Appellant argues that *In re Wands* stated that experimentation is permissible, and that they have provided an exemplary sequence that would be allowable; one of skill in the art could make the claimed nucleic acids (Brief pg 12-13).

However, given the lack of guidance in the specification for making nucleic acid encoding pesticidal proteins with 181, 217, 253 or 362 amino acid substitutions relative to SEQ ID NO:2, making and analyzing the claimed nucleic acid would require undue trail and error experimentation. The exemplary sequence itself does not provide guidance for making nucleic acids encoding proteins with such large numbers of substitutions.

Appellant argues that limiting the claims to only the exact exemplary sequences is unreasonable because it is relatively simple to modify a nucleic acid and amino acid sequence at a few positions to generate a protein that retains the full activity of the original, and would not give Applicant any meaningful protection; and claims to nucleic acids with 90% identity have been allowed in the past (Brief pg 14-15).

However, the ability of the public to successfully design around - to use the patent disclosure to design a product or process that does not infringe, but like the claimed invention, is an improvement over the prior art - is one of the important public benefits that justify awarding the patent owner exclusive rights to his inventions (*ATD Corp. v. Lydall Inc.* 43 USPQ2d 1170 (DC EMich 1997), 1178). Notice permits other parties to design around the patent (*London v. Carson Pirie Scott & Co.* 20 USPQ2d 1456 (CA FC 1991), 1458). Thus, Applicant's arguments

are without merit. Furthermore, If, as Applicant contends, it is "relatively simple" to modify 362 nucleotides, then it would also be "relatively simple" to modify 363 nucleotides, thus avoiding the scope of the claim. Thus, Applicant's argument about teaching the public to make and use the invention without obtaining any protection is contradictory to Applicant's argument that nucleic acids with 90% identity to SEQ ID NO:1 are enabled. Examiner cannot comment on the claims in issued patents.

Appellant argues that claims to nucleic acids with 93%, 94% and 95% identity would meet the patentability requirements even if specified percentages well below 90% and these claims were ignored in the previous actions (Brief pg 15).

However, nucleic acids with 93%, 94% and 95% identity to SEQ ID NO:1 encompass nucleic acid that encode proteins with 181, 217 or 253 amino acid substitutions relative to SEQ ID NO:2. The specification does not teach which 181, 217 or 253 amino acids of SEQ ID NO:2 to substitute. The claims were not ignored in the previous actions, as the previous actions stated that only claims to nucleic acids encoding SEQ ID NO:2 were enabled.

Appellant argues that the claims do not require that certain numbers of substitutions be made, but this is not the case - at least 90% sequence identity is required (Brief pg 15-16).

However, the numbers of nucleotide substitutions are drawn from the claimed percent identity. A nucleic acid with 90% identity to the 3621 nucleotide long SEQ ID NO:1 would have up to 362 nucleotide substitutions relative to SEQ ID NO:1. Nucleic acids with 90% identity to SEQ ID NO:1 could not be made without making 362 nucleotide substitutions. Such nucleic acids encompass those that encode proteins with 362 amino acid substitutions relative to the

1206 amino acid long SEQ ID NO:2. The specification does not teach how to make nucleic acids that that encode proteins with 362 amino acid substitutions relative to SEQ ID NO:2.

Appellant argues that those of skill in the art are aware of conserved regions of the Cry endotoxins and can use the Pfam database to determine protein function and conserved regions and regions that are more likely to tolerate mutations, as shown in the domain descriptions for Endotoxin N, M and C, each of which cites Li et al and Schnepf et al (Brief pg 16-17).

However, this database search provides no guidance as to the relevance to the sequence segments that are responsible for the pesticidal specificity of the proteins (see Li et al, pg 815, left column). Additionally, the Pfam database results sent by Applicant give no indication what, if any, of the information sent was available in the database at the time of filing. Lastly, the specification does not teach using this database.

Appellant quotes Li et al and argues that there is an extensive amount of information on Cry endotoxins to provide sufficient guidance to those in the art (Brief pg 17-18).

However, Li et al only provided guidance for making truncations and insertion of chymotrypsin cleavage sites; Li et al do not provide guidance for making 181, 217, 253 or 362 amino acid substitutions in a 1206 amino acid protein. Furthermore, the protein taught by Li et al is a cry3Aa protein, not a Cry8 protein.

Appellant argues that they cite Christians and Minshull to illustrate that it is customary to make and assay a number of sequences and is confused as to why Examiner speculated as to the outcome of experiments (Brief pg 18).

However, Christians et al did not produce proteins with only 70% identity to the starting protein (see paragraph spanning pg 260-261). Minshull et al teaches that a population should be

used as the starting material (pg 284, right column, paragraph 4); the specification does not teach such a population. Minshull et al also teaches that the activities of chimeric enzymes are not predictable simply by comparing those of the parent enzymes (paragraph spanning pg 288-289); thus, even if the population of starting materials has been provided, making nucleic acids that encode proteins pesticidal to coleopterans and have substitutions within the full scope of the claims is not predictable. Examiner speculated as to the outcome of experiments because that is part of the enablement analysis - do the experiments produce predictable results and is the experimentation necessary to achieve the desired outcome undue? In the instant case, the results are not predictable and the amount of experimentation is undue.

Appellant argues that the amount of experimentation would not be undue, given the teachings in the specification, and Lazar and Hill demonstrate this (Brief pg 18-19).

However, Lazar and Hill teach that even making single amino acid substitutions is unpredictable; Hill teaches that is true even the substitutions are made based on comparison to homologous sequences. Thus, making 181, 217, 253 or 362 amino acid substitutions relative to SEQ ID NO:2, as encompassed by the full scope of the claims, would be even more unpredictable.

**(b)** Claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52 and 55-64 do not meet the written description requirement of 35 USC §112, first paragraph.

Appellant argues that the claims are not require the modification of particular numbers of nucleotides, only that the nucleic acids have a certain percent identity to SEQ ID NO:1 (Brief pg 20).

However, the numbers of nucleotide substitutions are drawn from the claimed percent identity. A nucleic acid with 90% identity to the 3621 nucleotide long SEQ ID NO:1 would have up to 362 nucleotide substitutions relative to SEQ ID NO:1, and could encode a protein with 362 amino acid substitutions relative to the 1206 amino acid long SEQ ID NO:2. Three hundred sixty-two nucleotide substitutions and 362 amino acid substitutions must be described to describe nucleic acids with 90% identity to SEQ ID NO:1.

Appellant argues that they have provided an exemplary sequence, SEQ ID NO:1, the claimed nucleic acids are defined in relation to SEQ ID NO:1, they have provided a structural definition of the sequences, and because they have provide assays for one of skill in that to assess whether those sequences meet the functional limitation of the claims, they have met the requirements of *Eli Lilly* and *Amgen*, also citing *Amgen vs Hoechst*, *Moba* and *Enzo* (Brief pg 21-22).

However, *Eli Lilly* at pg 1406 states "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." A single nucleic acid of SEQ ID NO:1 does not constitute a significant portion of the vary large genus of nucleic acids with 90% identity to SEQ ID NO:1. The specification does not describe the structural features that distinguish nucleic acids with 90% identity to SEQ ID NO:1 that encode pesticidal proteins from nucleic acids with 90% identity to SEQ ID NO:1 that do not encode pesticidal proteins or pesticidal proteins with 362 amino acid substitutions relative to SEQ ID NO:2 from nonpesticidal proteins with 362 amino acid substitutions relative to SEQ ID NO:2.

*Enzo* states that a deposited sequence meets the written description requirement; no nucleic acid with 90% identity to a known sequence and that encodes a protein with 70% identity to the original protein has been deposited by Applicant, nor has any other nucleic acid within the scope of the claims. In the instant case the knowledge of the art the disclosed function is not sufficiently correlated to a particular, known structure; which 362 amino acids can be substituted in SEQ ID NO:2 is not described in the specification or the art.

Appellant argues that Bt toxins are very well-characterized, and that the specification uses Li et al for guidance in making mutations in the Cry8-like proteins, as in Example 6; thus, adequate guidance is provided (Brief pg 22).

However, Li et al only provided guidance for making truncations and insertion of chymotrypsin cleavage sites; Li et al do not describe making 362 amino acid substitutions in a 1206 amino acid protein. Additionally, Applicant's arguments are drawn to an enablement rejection, not a written description rejection.

Appellant argues that one of skill in the art could use the Pfam database to make the claimed nucleic acids, thus they have envisioned the detailed construction of the gene (Brief pg 23).

However, the specification does not describe the necessary and sufficient structural features for nucleic acids with 90% identity to SEQ ID NO:1 and that encode a protein that is pesticidal to Coleopterans within the full cope of the claims, and from what was sent in Appendix B, neither does the Pfam database. The Pfam database results sent by Applicant give no indication what, if any, of the information sent was available in the database at the time of

filing. Additionally, Applicant's arguments are drawn to an enablement rejection, not a written description rejection.

Appellant argues that the specification describes several nucleic acids with low percent identity to SEQ ID NO:1 but that encode pesticidal proteins. In Examples 4 and 6, truncated proteins encoded by SEQ ID NO:15 and 19 are described; they have 55% and 51% identity to SEQ ID NO:1, respectively. Example 6 also teaches the truncated protein encoded by SEQ ID NO:11 which also has a four amino insertion in it; SEQ ID NO:11 has 56% identity to SEQ ID NO:1. Applicant also argues that the specification teaches a maize-optimized sequence, SEQ ID NO:9, which encodes SEQ ID NO:16 but has less than 69% identity to SEQ ID NO:15 (Brief pg 23-24).

However, the fragments and variant taught in the specification are not sufficient to describe nucleic acid within the full scope of the claims. While the query match similarity may be 55%, the query match value is affected by differences in length of the sequences; see the discussion above in the response to the enablement rejection. No amino acid substitutions were made in the protein sequence encoded by SEQ ID NO:15, thus, this nucleic acid does not describe nucleic acids encoding proteins with 181, 217, 253 or 362 amino acid substitutions relative to SEQ ID NO:2.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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